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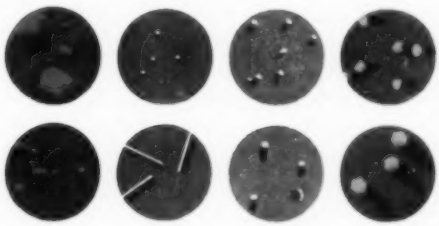

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ALBRO C. GAYLOR, *Publisher*
ROSE E. BODET, *Assoc. Publisher*

JOHN FITCH LANDON, *M.D., Editor*

Vol. 78 No. 1

January 1961

CONTENTS

Entered as second class matter Feb. 5, 1892, at New York, N. Y., P. O. under the Act of March 3, 1879.

Published monthly since 1884.

Subscriptions: one year—$7.50; two years—$12.00; three years—$16.00.

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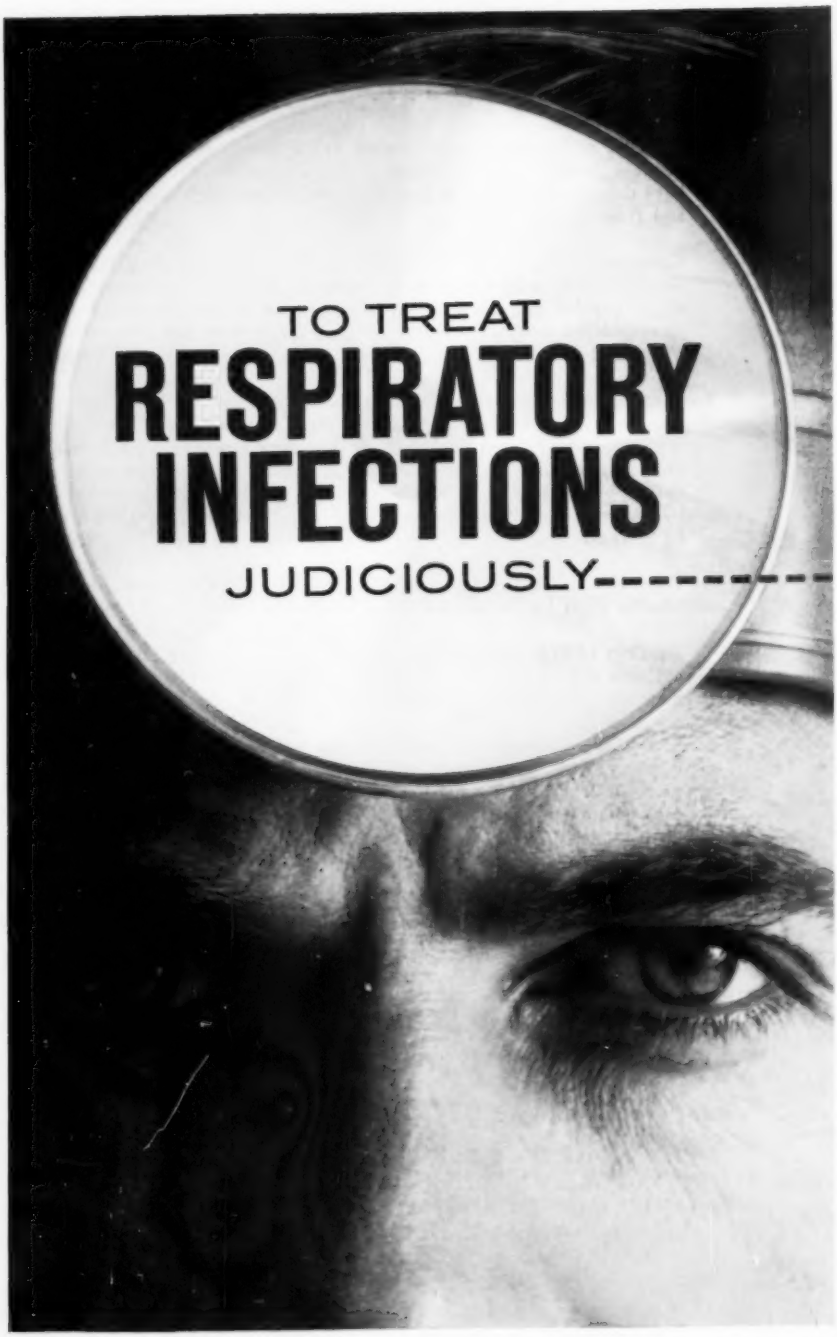
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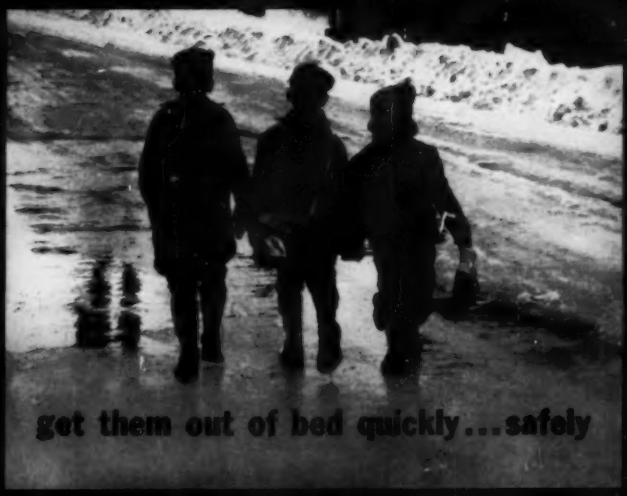

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guest editorials

Preventive Medicine in Pediatrics

CONRAD M. RILEY, M.D.*
COLORADO

To an audience made up of those engaged in Pediatrics, a discipline which has long prided itself on its concern about prevention of disease and disability, it may seem redundant to exhort readers to reconsider this problem. On the other hand, as certain areas have been studied and conquered the former distant horizons have now come into the foreground and new unsuspected potentially obtainable goals loom on the horizon in the background.

Among achievements already accomplished a few mileposts can be mentioned. Probably among the earliest successful effort along lines of prevention was the introduction of vaccination against smallpox. The subsequent development of microbiology with its identification of disease producing agents coupled with the growing concept of immune response gave rise to the now widely practiced procedure of immunizing children against many microbe or virus induced infections.

Epidemiological studies in conjunction with experimental laboratory work and field work gave tools with which sources of infection or of noxious chemical materials could be eliminated by new approaches to sanitation. Witness the virtual disappearance of typhoid fever, cholera and malaria from large areas of the world as well as reduction in incidence of lead poisoning. That such practices are not world wide is to be deplored, but once the potential has been discovered, one can hope that it can be made to spread into even the most remote fringes of the human population.

Students of nutrition have broadened the area of understanding of essential food requirements so that in enlightened communities Vitamin D deficient rickets and scurvy are no longer seen. Re-

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search into the possible harmful effects of some traditionally acceptable food substances is underway and if the present suggestive findings are borne out we may find the national menu changing drastically as centenarians swell the work of the census takers.

Such matters discussed above are affairs quite well in hand. But other matters off in the middle ground of our preventive picture are beginning to come under scrutiny. Since they are beyond our immediate vision, the outlines are less distinct and a concept of what sort of satisfactory answers can be found is as difficult to form as might have been the case for a 19th century doctor trying to conceive of what could be done about diphtheria.

In this area of attempting to control potentially harmful environmental factors with imperfect knowledge of appropriate techniques is the pediatrician's self-appointed role as advisor to young parents in the art of child rearing. The fact that the pendulum has swung from an attitude of rigid management to complete permissiveness and part way back again attests to the fact that, though the need is recognized, the answers are still not at hand.

One of our greatest killers in childhood today is accidents. At present the only comfort we can take is that there is organized study of this threat and intelligent research is being carried out. Emotional maladjustment, so common in the adolescent age, used to be something to be suppressed with firmness. More recently it has been a source of hand-wringing worry. And currently it is an area of intense study with more and more "adolescent clinics" springing up throughout the country.

The study of frank mental illness both in children and adults has become a respectable area in which foundations like to give support. Preventive psychiatry, however, has only begun to be included in areas suitable for investigative work. The attempt to show how psychological disturbance could produce organic disease has enjoyed much prominence. The converse, showing the effect of organic illness on the psyche, has had less formal attention, but this too is being surveyed by research-oriented professionals. Out of all these approaches may eventually come as exciting programs of prevention of psychogenic disability as the control of smallpox.

The present healthy growth and development of the infant science, human genetics, has already begun to color the thinking of physicians who have an eye to prevention. Though dreamers

project the hope that manipulation of the chemical structure of genes might eventually be possible, the truth is that even now genetic counseling service is becoming ever more widely attempted. Imperfect as present efforts along these lines may be, the fact that such projects are already initiated augurs well for the future development of this type of disease control.

A final area to be mentioned has received some recognition through the popularization of a Greek derived expression, "iatrogenic disease", but little in the line of formal research into this type of preventable disorder has been inaugurated. What doctors can do to or for their patients for good or evil has not been studied with the coldly scientific approach as intensively as it could and should be. In general our profession accepts itself as a strictly beneficent group unfortunately studded with a few frank backsliders with obviously evil intent. That a man of goodwill could or would unintentionally harm his patient has been given no organized consideration. Certain fairly obvious examples come to mind such as the ill advised use of drugs with which too little experience has been available to demonstrate unsuspected hazards; surgical procedures such as tonsillectomy which may have facilitated the development of bulbar polio in some children; inappropriate exposure of pregnant women to ionizing radiation, or to injudicious hormone administration. In addition to these physical or chemical insults there have also been emotional traumas inflicted by well intentioned physicians. The example of cardiac cripples with organically sound hearts, persons with cancerophobia and pseudo-vitamin deficient subjects are all too prevalent thanks to some doctors and their allies in the pharmaceutical industry and in health foundations. Thus the medical profession itself is a source of disease which study and evaluation may help to prevent.

In short we have come a long way in medicine in our ability to prevent formerly inevitable scourges. We are currently struggling with some problems that may yield to the preventive approach. And now there are many areas coming into sight which deserve greater investigation and hold promise of allowing as great conquests in the future as have already been recorded in the past. In pushing forward this concept of even greater prevention, the medical profession must not absolve itself from the close scrutiny it is leveling at how environmental factors can affect the health of individuals and even of communities. The field of Preventive Medicine, far from growing narrower as past victories are tabulated, is in fact growing broader and broader.

Serum Glutamic Oxalacetic Transaminase Activity in Health and Disease in Pediatrics

M. Diwany, M.R.C.P.,* M. Talaat, Ph.D.,* M. Gabr, M.D.,*
N. Mokhtar, M.D.,* Y. A. Rahman, M.D.*

Egypt

A TRANSAMINASE is an enzyme which catalyzes the interconversion of an aminoacid with a ketoacid. There are many such enzymes, with varying degrees of specificity for substrate. The simplest ones to assay are those which involve an easily measurable intermediate such as oxalacetic acid or pyruvic acid.

Serum glutamic oxalacetic transaminase is present in all tissues with highest concentrations in the myocardium, liver, skeletal muscle, brain, kidney and red blood corpuscles.[1,2] Under normal conditions, very little activity can be demonstrated in the blood, as the enzyme is mainly intracellular, but when the cells disintegrate the enzyme is released resulting in increase in serum activity.[3] Clinical interest in serum transaminase determination started in 1955 when La Due and Wroblewski[4] demonstrated its increase in recent cardiac infarction. Since then, many authors have estimated the activity of serum transaminase in various diseases and it is now evident that pathological alteration in transaminase activity can be produced by cardiac disease,[3,4,5] liver disease,[6,7,8,9] muscular disease,[11,12,13] shock or any acute hemolysis.[14]

In view of the paucity of the reports on the value of serum transaminase activity in the pediatric age group this work was undertaken with the aim of establishing normal values for infants and children and to evaluate serum transaminase variation in various pathological conditions in childhood.

METHOD

The method used was the calorimetric method of Dubach.[2] The accuracy of the method was repeatedly checked by duplicate determinations in several subjects. The principle of the method is to measure the pyruvic acid liberated from the substrate (Reagent A) by enzymatic activity of the serum. This is to be compared with a

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blank in which the enzymatic activity is blocked prior to addition of the substrate.

Since the method is not readily available in the American literature, a short description of it is presented. Six reagents are used.

Reagents:

1—Reagent A: The transaminase substrate:

- D L aspartic acid 2.66 gm.
- potassium hydrogen phosphate 2.00 gm.
- alpha Ketoglutaric acid 0.6 gm.

dissolved in normal potassium hydroxide solution, and solution adjusted to PH 7.4 using PH meter, and kept in a refrigerator at 1-5° C.

2—Reagent B: Trichloracetic acid 100%.

3—Reagent C: 5 gm. citric acid ($C_6H_8O_7 + H_2O$) dissolved in 5 cc. water, and 5 cc. aniline added.

4—Reagent D: 100 mgm. of 2-4 dinitrophenylhydrazine, dissolved in 20 cc. of conc. Hcl (37%), and 80 cc. water.

5—Reagent E: Toluene.

6—Reagent F: 2.5 gm. potassium hydroxide dissolved in 100 cc. 95% Alcohol, to be freshly prepared.

Technique:

1—0.5 cc. serum is added to each of 2 test tubes (reaction and blank tube).

2—One drop of reagent B is added to the blank tube; this precipitates the proteins and inactivates the enzyme. A drop of reagent C is then added and the tube shaked thoroughly.

3—0.5 c.c. of reagent A is added to each tube, and left to stand for 20 minutes at 25 ± 2° C.

4—To the reaction tube, one drop of reagent B is added, and a drop of reagent C is added. The T.C.A. acid precipitates the proteins and arrests the enzymatic action. The addition of aniline citrate produces pyruvic acid. The tube is shaken vigorously and left to stand for at least 20 minutes.

5—0.5 cc of reagent D is added to each tube, the tube is shaken and left for 4 to 6 minutes.

6—2 cc. of reagent E is pipetted in each tube, the tubes are shaken in a mechanical shaker for ½ minute, (to ensure that all the dinitrophenyl hydrazone pyruvate is extracted) then centrifuged for 7 minutes.

7—One cc. of the supernatent toluene solution is taken from each tube and run in a separate marked test tube.

8—Three cc. of reagent F are added to each tube to produce the red color complex. The red solution is poured in photometer cell and its extinction is measured using a filter with a range of 450-550. Prior to this measurement the photometer is set at zero extinction using the blank.

9—A reference curve is constructed using a series of aqueous pyruvic acid solution ranging from 10–500 gamma/cc.

The extinction is plotted along the ordinate against the pyruvic acid along the abscissa.

Serum glutamic oxalacetic transaminase is measured in units/ml serum. One serum GOT unit is defined as the activity of one cc. serum which will form the same amount of color complex in 20 minutes at $25 \pm 2^{\circ}$ C as one gamma/cc. of pyruvic acid.

CLINICAL MATERIAL

102 determinations were performed in 85 subjects. The subjects investigated were grouped into two groups.

Group I: included 46 normal infants and children. Their age ranged from one day up to 12 years. This group included six newborn babies aged, 2, 3, 5, 6, 12 and 26 days. The subject was considered normal if he was not suffering from any present or past ailment that may affect the level of serum transaminase activity.

Group II: included 39 children suffering from the following diseases: Muscular disorders (12 cases), hepatic disorders (6 cases), rheumatic fever (7 cases), hemolytic anemia (5 cases), juvenile diabetes (5 cases) and marasmus (4 cases). All subjects were subjected to complete clinical examination. The appropriate investigations were done on the different patients including liver function tests, liver biopsy, muscle biopsy, electrocardiographic and radiological examination.

Serial determinations of serum transaminase were done in two newborn infants, two cases of infective hepatitis and three cases of acute hemolytic anemia.

RESULTS

Group I: Table I shows the level of serum transaminase activity in 40 normal healthy infants and children.

TABLE I

Age group: 3/12-2 yrs.				2 - 5 years				5 - 12 years			
Case No.	Age	Sex	S.got	No.	Age	Sex	S.got	No.	Age	Sex	S.got
1	3m.	F	12	7	3	F	30	76	6	F	32
2	6"	F	25	11	3	M	30	51	6	F	25
10	2yr.	M	12	21	3	F	32	5	7	F	25
65	2"	M	34	22	3	M	25	6	7	F	33
				35	3	F	18	23	7	F	30
				44	3	F	33	47	7	F	33
				36	4	F	30	50	7	M	12
				42	4	F	18	59	7	M	34
				37	5	F	25	60	9	F	25
				41	5	F	36	62	9	F	10
				45	5	M	32	68	10	M	25
				58	5	M	23	69	10	F	32
				75	5	F	20	70	10	M	25
				52	5	F	10	71	10	F	12
								27	10	M	30
								26	10	M	20
								72	10	M	36
								34	10	M	14
								39	10	M	8
								40	10	M	35
								19	12	F	12
								12	12	F	36
Range			12-34				10-36				8-36
Mean			20.75				25.3				24.3

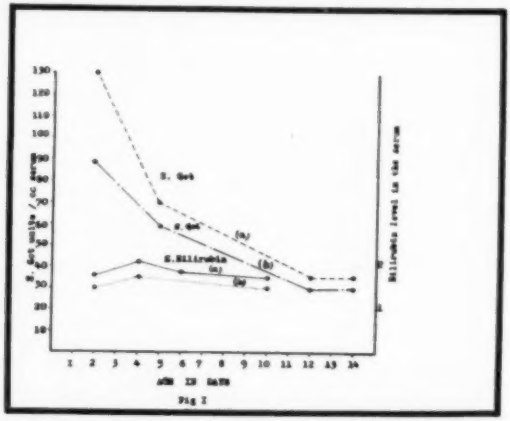
It is evident from table I that the serum transaminase values in the 40 normal subjects studied ranged from 8 – 36 units; the mean value was 24.65 units. These individual variations in the level of the enzyme were not related to either sex or age.

Table II shows the level of serum transaminase activity in six newborn infants (2 - 26 days).

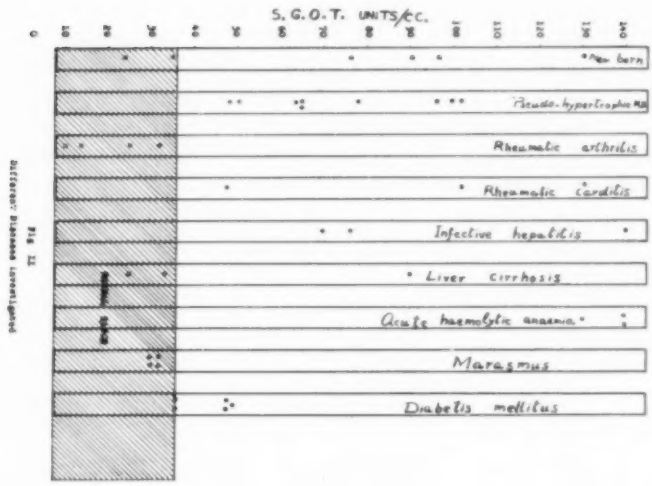
Table II.

Case No.	Age	Sex	S. got
8	6 days	F	76 units
18	12 "	F	79 "
38	5 "	M	24 "
57	26 "	M	35 "
20	2 "	F	130 "
46	2 "	F	90 "

It will be seen that the level of the enzyme in the six newborns varied from 24 to 130 units. Levels above the normal range were found in four out of the six cases. Follow up studies of enzymatic activity were done in two of these babies in an attempt to find out the postnatal rate of decline of the enzymatic activity. Serial esti-



mations of serum bilirubin and complete blood picture were also done. The results are diagrammatically represented in figure I. It is evident from figure I, that there was a gradual decline in the activity of the enzyme in the first few days of life. In case No. 20 serum transaminase activity was 130 units at 2 days, 70 at 5 days and by the age of 12 days the enzymatic activity dropped to normal value and remained thereafter at the low level. Case No. 46 showed almost the same changes, the level of the enzyme reaching normal value at the age of 14 days. There was no relation between the level of enzymatic activity and serum bilirubin or R.B.Cs. count.



Group II: The results in various pathological conditions are presented in figure II and tables 3, 4, 5, 6. Table III shows the serum transaminase activity in some muscular disorders.

Table III.

Case No.	Age	Sex	Diagnosis	Duration of dis...	S.got	Muscle biopsy
16	11.5 years	M	Pseudohypertrophic muscular dystrophy	3 years	49	Pseudohypertrophic muscular dystrophy.
17	15 "	M	" "	4-5 "	65	" "
30	6 "	M	" "	1.5 "	100	" "
58	6 "	M	" "	1 "	102	" "
61	12 "	M	" "	3 "	96	" "
63	10 "	F	" "	3 "	78	-
64	5 "	M	" "	1 "	65	" "
66	7 "	M	" "	2 "	64	-
67	8.5 "	F	" "	1.5 "	50	-
54	8 "	F	Fascio scapulo humeral		35	-
32	12 "	F	Peroneal muscular atrophy.	5 "	36	Peroneal muscular atrophy.
31	8 months	F	Polymyositis.		60	Polymyositis.

The group of patients studied included 9 cases of pseudo-hypertrophic muscular dystrophy, one case of fascio-scapulo-humeral type, one case of peroneal muscular atrophy and one case of polymyositis. It is evident from these results that all cases of

pseudohypertrophic muscular dystrophy had elevated values of serum transaminase with readings ranging from 48-102 units. The higher values were obtained in cases with more generalized muscular involvement. The cases of peroneal muscular atrophy, and fascioscapulohumeral type of muscular dystrophy showed a normal level of the enzyme. The serum transaminase level in the patient with polymyositis was 60 units.

Table IV shows the serum transaminase level in children suffering from rheumatic fever.

Table IV.

Case No.	Age yrs.	Sex	Diagnosis	S.got	Remarks
7	12	M	Rheumatic arthritis	14	No clinical, radiological or E.K.G.evidence of cardiac involvement.
19	8	M	" "	32	
53	6	F	" "	25	
55	7	M	" "	10	
33	5	M	" myocarditis	48	Dyspnea on exertion.
29	10	F	" " ,D.M.	102	Orthopnea.
15	10	M	" " "	130	Orthopnea.

The results illustrated in table IV show that the serum transaminase activity of cases suffering from rheumatic arthritis was within the normal range, while in cases complicated with myocarditis there was an increase in serum transaminase activity. It was noticed that the increase in the activity of the enzyme was proportional to the severity of the cardiac involvement as judged by the clinical manifestations and laboratory investigations.

Table V illustrates serum transaminase activity in children suffering from various hepatic affections.

The group included three patients with infective hepatitis, one of whom running a subacute course and three cases of liver cirrhosis. It is evident from table V, that the patients with infective hepatitis showed marked elevation of serum transaminase activity. Serial estimations of enzymatic activity in these patients showed that decrease of the level of serum transaminase paralleled clinical improvement of the patients. Normal values of the enzyme were attained after approximately one month in cases No. 4 and 3 while in case No. 9 with a subacute course, high levels of the enzyme were still present 7 months after the onset. In the three cases of liver cirrhosis investigated, two cases showed normal values of serum transaminase, the third case showed a high

level of 90 units. It is of interest that this latter case of liver cirrhosis showed recent hemorrhagic necrosis in biopsy while the others did not.

Table V.

Case No.	Age yr.	Sex	Diagnosis	Duration from onset	S.got	Liver biopsy	Remarks
3	4	M	Infective hepatitis	3 days 4 wks.	74 U. 38	-	marked clinical & laboratory improvement, after 4 weeks.
4	7	F	Infective hepatitis	3 days 2 wks. 3 " 4 "	140 80 48 38	-	marked clinical & laboratory improvement after 4 weeks.
9	3	M	Infective hepatitis	7 months	70		Progressive enlargement of the liver with persistent clinical and laboratory evidence of hepatic affection 7 months ago.
12	3	F	Liver cirrhosis	1 year	38	post necrotic hepatic cirrhosis	History of infective hepatitis one year before.
24	3,5	F	Liver cirrhosis	7 months	38	Post infective hepatitis.cirrhosis.	History of infective hepatitis 7 months ago.
28	1,5	F	Liver cirrhosis	6 months	90	Post necrotic liver cirrhosis with recent haemorrhagic necrosis.	Cirrhosis of unknown etiology general condition , poor

Table VI shows the serum transaminase level in children suffering from hemolytic anemia.

This group included three cases of acute hemolytic anemia, and two cases of chronic hemolytic anemia. The three cases of acute hemolytic anemia were aged 1.5-2 years. The hemolytic attack (which was their first attack) was sudden, severe and associated with hemoglobinuria. They were seen 2-6 hours after the hemolytic episode, with severe pallor, dyspnea and a palpable spleen. The hemoglobin ranged from 3-5 gm. %, the serum bilirubin was elevated, while the Coomb's test was strongly positive in one case and weakly positive in the other two cases. All three cases received

TABLE VI

Case No.	Age yr.	Sex	Diagnosis	S.Got	Remarks
14	2	M	Acute hemolytic anemia	130	dropped to normal after 72 hours
28	1,5	M	" " "	140	dropped to normal after 48 hours
43	2	M	" " "	140	" " " " "
73	6	F	Cooleys anemia	40 U.	increased to 140 U during an acute hemolytic exacerbation.
98	2	M	Von Jaksch's syndrome	60 U.	

blood transfusion and corticosteroid therapy, (after the initial blood sample for S. Got determination was taken), with a fairly rapid recovery. Of the two cases with chronic hemolytic anemia

one case was a typical Cooley's anemia, while the other case, a boy aged 2 years suffered from a chronic hemolytic process with splenomegaly, rickets, a serum bilirubin of 2.5 mgm. % and leucocytosis.

As is evident from table VI serum glutamic transaminase activity was raised in all three cases of acute hemolytic anemia (samples were taken 2-6 hours after the onset of hemolysis). The serum glutamic oxalacetic transaminase activity, however, dropped to normal values 48-72 hours after the acute stage. In the two cases of chronic hemolytic anemia the S. Got activity was slightly raised except during an acute hemolytic exacerbation in case No. 73 (Cooley's anemia), when it was found to be 140 units. This sample was taken 12 hours after the acute hemolytic episode.

The results of diabetic children investigated (fig. II) showed that the serum transaminase activity was normal in two subjects (36 & 36 units) and was slightly elevated in the remaining three patients (48, 49 & 49 units).

The four cases of marasmus showed a normal level of serum transaminase (fig. II).

DISCUSSION

In a series of 40 normal children aged three months to twelve years, serum glutamic oxalacetic transaminase activity was found to vary from 8-36 units; the mean value being 24.65 units. These figures fell within the normal adult range as estimated by the same method in the Physiology Department.[15] There was no relation between serum transaminase activity and the sex or age of the children investigated. These results are in agreement with previous reports.[14]

The results for normal newborns examined showed much higher figures specially with the younger infants, ranging from 24-130 units. These higher values in newborns were reported by other investigators.[16,17,18] Several explanations were put forward; immature liver function,[18] hemolysis and trauma to tissues incident to birth.[14] The level of transaminase activity was followed up by serial determinations in two newborns, and was found to fall to normal values within 12-14 days. The delayed drop of serum transaminase activity in newborn infants is totally different from the more rapid drop which occurred following acute hemolytic anemia, proving that hemolysis alone cannot be responsible for

the high transaminase levels in newborns. Other contributory factors either increasing the production of the enzyme or decreasing the rate of its removal from the blood or both may be involved. Kove[18] suggested that immaturity of the liver in the newborn is a contributing factor. It is however difficult to explain how immaturity of the liver would raise the serum transaminase level in the absence of cell destruction, and there is no evidence that normal liver tissue is responsible for inactivation of transaminase. Involution of the left lobe of the liver is known to occur during the first week after birth.[19] In our opinion this involution of the left lobe may play a role in the raised transaminase activity in the newborns. Since little is known about the mechanism of clearance of the enzyme, it is difficult to ascertain the role of delayed elimination of the enzyme, if it exists, as a cause for the elevation of serum transaminase in the neonatal period.

The value of estimation of serum transaminase as a liver function test and as a guide for follow up of progress in infective hepatitis is well established.[9,10] Only a few cases of liver disease were thus investigated. It is evident from table V that in cases of liver cirrhosis, the serum transaminase level parallels the degree of cellular necrosis as evident pathologically. Thus case No. 25 with associated cellular necrosis showed high level of the enzyme while in the other two cases without pathological evidence of necrosis, serum transaminase activity was normal.

The results of serum transaminase activity in children with rheumatic fever confirm earlier suggestions[2] that it is raised in the presence of carditis. Normal values of serum transaminase were present in the four children with rheumatic arthritis but without clinical carditis (10-32 units) irrespective of the degree of the severity of the arthritic lesion as judged by routine laboratory methods. On the other hand serum transaminase was persistently elevated in all children with cardiac involvement (48-130 units). The level of the enzyme seemed to be related to the degree of cardiac involvement. Serum transaminase determination might thus prove to be a useful adjuvant test to judge the presence and degree of cardiac involvement in rheumatic fever.

Serum transaminase activity was estimated in children with various muscular disorders. It was elevated in all cases of pseudohypertrophic muscular dystrophy, the level of the enzyme being related to the extent of muscular involvement. This is in agree-

ment with reports of previous investigators.[11,12,13] The normal level of the enzyme in the child with fascioscapulohumeral type might be due to the slower course of the disease in that type, since the rate of enzymatic release reflects in part the rapidity of the process and in part the amount of tissue involved. Slight elevation in serum transaminase activity was found in the case of polymyositis. Murphy and Cherniak[13] reported normal or borderline values in polymyositis while Seikert and Fleisher[11] found increased activity of the enzyme in two out of three patients.

The results of serum glutamic oxalacetic transaminase determination in hemolytic anemia are interesting. It has been reported that S. Got is essentially normal or minimally elevated in hemolytic disorders except in acute hemolysis.[14] In our three cases of acute hemolytic anemia the hemolytic process was severe and was associated with marked hemoglobinuria, denoting intravascular hemolysis. The high serum glutamic oxalacetic transaminase levels in these cases is thus explained by the liberation of the enzyme from the destroyed erythrocytes into the serum. The quick decline of the S. Got to the normal level within 48-72 hours in these cases indicates the rapidity of the mechanism of clearance of the enzyme. In the two cases of chronic hemolytic anemia, where hemolysis takes place more gradually in the spleen, liver, or R.E.S., serum glutamic oxalacetic transaminase activity is only slightly raised. In these cases, anoxic liver damage from the long standing anemia might be a contributory factor in the slightly elevated S. Got values.

Normal levels of serum transaminase were found in four marasmic infants. High normal or slightly elevated levels of serum transaminase activity were found in diabetic children conforming with the results in diabetic adults reported by Donato in 1957.[21]

SUMMARY AND CONCLUSIONS

1. Serum glutamic oxalacetic transaminase is a relatively simple test to perform in pediatrics. Normal levels in children of various ages (except newborns) are similar to adult values (8-36) units.
2. Newborn infants show higher levels of serum transaminase which decline gradually towards normal within the first two weeks of life. The various factors involved in this elevation are discussed.
3. Studies of serum transaminase activity in acute hemolytic

anemia revealed that S. Got was raised in three cases with sudden and severe intravascular hemolysis. This rise however was transient, lasting 48-72 hours, indicating the rapidity of the mechanism of clearance of the enzyme. S. Got was slightly elevated in chronic hemolytic anemia.

4. S. Got was estimated in various pathological conditions. It was found to be normal in marasmus and diabetic children. It was found to be high in pseudo-hypertrophic muscular dystrophy and slightly elevated in one case of polymyositis. It was normal in one case of fascio-scapulo-humeral muscular dystrophy. S. Got was found to be raised in cases associated with hepatic necrosis and rheumatic carditis. It seems to be a useful laboratory test in the diagnosis and follow up of liver disease and rheumatic myocarditis.

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Extreme Hydrocephalus* — A Clinical Report

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This patient S.C.R., age 7½ years, was admitted to the Fort Wayne State School 9/5/59. The mechanism of labor was "quite routine and normal." The mother stated that the head, while tremendous in size, had not increased greatly in 2 years. (Fig. 1)

Examination: The child had an extreme degree of hydrocephalus. The occipito-frontal circumference of the skull measured 99 cm. Dimensions of the anterior fontanel were 12 x 18 cm., and of the posterior fontanel 5 cm. x 9 cm. There were decubitus ulcers present, particularly over the occipital area. (Fig. 2)

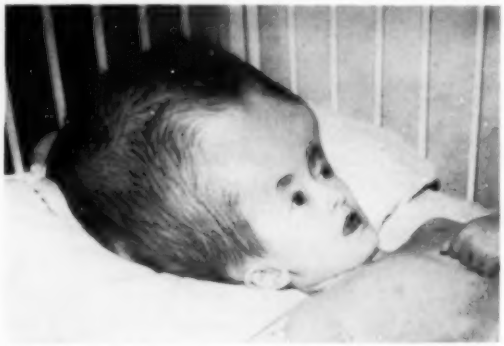

FIG. 1. Photograph of patient showing the marked enlargement and deformity of the head.

Examination of the fundi showed optic atrophy with no essential change in vasculature. The optic discs were very small. There was a constant lateral nystagmus. A mild respiratory infection was present with evidence of rhinitis and moderate degree of tracheal infection. The extremities were flaccid with marked hypotonicity and sluggish reflexes. No contracture was noted at any level. The child was playful, responded to words, and accepted objects handed to him. Only on one occasion, October 5, 1959, were seizures noted. During this time he was treated with Dilantin, 0.1 gm., b.i.d.

*From the Fort Wayne State School, Fort Wayne, Indiana (B. Dolnick, Superintendent). (Dr. Meyer) Clinical Director; (Dr. Stadler) Consultant in Pediatric Neurology.

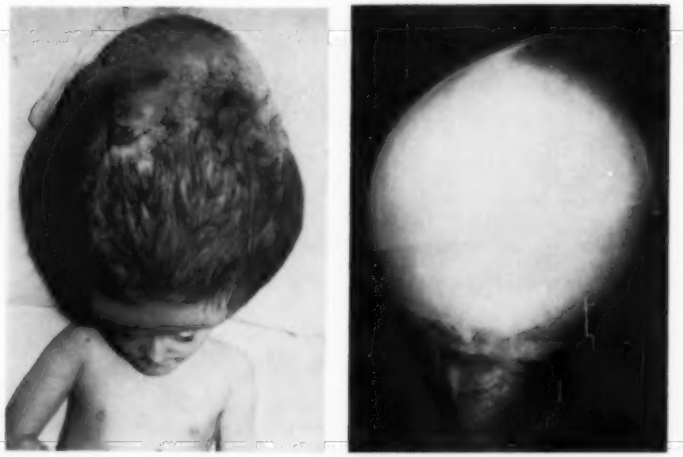

FIG. 2. X-ray of skull of patient showing huge enlargement. The transverse line noted is an artefact since it was necessary to x-ray the skull in two portions using lead markers

Laboratory: Serologic test for syphilis was negative. Fasting blood sugar was 84 mg. % and blood urea nitrogen was 12 mg. %. Microhematocrit was 33 vol. % and leukocyte count 7,400 per cubic mm. of blood with hemoglobin of 8 grams. Except for changes attributable to anemia, the blood smear showed no abnormality. X-ray of the wrist revealed no abnormality although the bone age was approximately 2 years retarded. The EEG suggested a slightly greater degree of dysfunction on the right. (Fig. 3)

Mental Level and Reactions: The child appeared severely retarded. He exhibited considerable interest in his environment and responded to words from the examiner and ward attendants. He appeared ready to start a game of throwing a plastic dish over the side of the bed and have it retrieved in order to toss it out again. Hand co-ordination seemed quite adequate. He appeared happy and laughed heartily and used such phrases as "bye-bye" and "plastic dish." Articulation was not good. The attendants called attention to the fact that additional verbalization had been noted. Because of his pleasant personality, the main essential problem in his care involved the prevention and treatment of the decubitus ulcerations of the scalp, particularly the occiput.

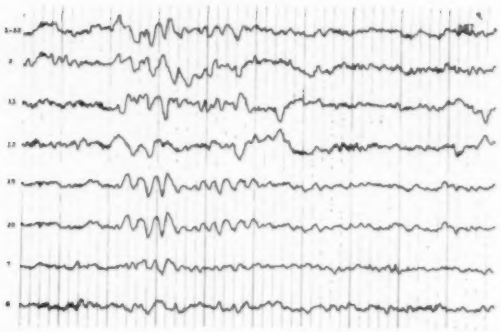

FIG. 3. Representative portion of the EEG. An alpha rhythm is not evident. There are occasional rhythmical six-cycle-per-second forms seen posteriorly. The record is obscured by muscle and movement artefacts during most of the alert stages. Drowsiness is evident during the latter portions of the recording, the slowing being reasonably symmetrical. A discrete focus is not seen. Seizure activity is not present. A suggestion of asymmetry is noted on the right.
Clinical Interpretation: The changes in this record reflect a moderately severe degree of generalized cortical impairment. There is perhaps a slightly greater degree of dysfunction on the right, but this is not definite. The changes present are non-specific in character. A discrete focus was not evident. Seizure activity was not seen.
Diagnosis: Dysrhythmia, Grade II, Generalized.

Several examiners felt that stability or arrest of the hydrocephalus had not occurred. Measurements confirmed this. On September 23, 1959, measurement of the head was 94 cm. in the occipito-frontal circumference. On May 18, 1960, this same measurement was repeated and found to be 99 cm. (see above) Pressure changes in the open fontanels were remarkably minimal in view of the tremendous degree of hydrocephalus.

SUMMARY

A case report is given of an 8 year old white male with an extreme degree of hydrocephalus. It seems as though progression of the enlargement is still apparent.

A striking feature is the degree of mentation or cerebral activity maintained. A happy personality, ready to play and laugh, he successfully conceals the real degree of mental retardation.

The X-ray of the skull gives an idea of the paper-thin layer of cerebral cortex present. With this minimal cortical tissue, the patient is able to enjoy life and even learn.

We are also indebted to Mr. Andrew Weber, M.T. (X-ray laboratory) and Dr. Glenn Brinker (Photography) for their technical assistance.

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Poison Control

DEXEDRINE, METALLIC MERCURY, ARSENIC AND ARNICA INTOXICATIONS

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Substance Ingested: Dexedrine *Age*: 19 years

The patient, who is a baker, reportedly worked for 16 hours without sleep prior to the accident. One of his coworkers, who had been taking Dexedrine for weight reduction, gave him one tablet so that he might keep awake. After taking the medication, he felt better and took another tablet. Immediately, he began to have chills and fever, vomited, and became disoriented.

Upon admission to the hospital, no other symptoms were observed. He was sent to Queens General Hospital and transferred to Kings County Hospital for psychiatric observation, where he remained for two days.

This unusually severe reaction to a moderate dose of Dexedrine should serve as a deterrent to individuals from offering their medications to others. This was a permanent lesson to the victim because of the resulting traumatic reaction from his sojourn in a psychiatric institution, both to himself and to members of his family.

Substance Ingested: Metallic Mercury *Age*: 1½ years

Dr. Philip Lustbader, a pediatrician from Brooklyn, reports an interesting case of mercury ingestion as follows:

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"At home the child obtained a thermometer and broke it in her mouth. Just the lower part containing the mercury was broken. The family doctor was called by the mother, who had just seen what her child had done. This happened at 10:00 A.M. and the child was examined by the family doctor and referred to me, to be seen in the afternoon.

"On examination, the child was in no distress and quite active. Examination of the oral cavity revealed no lacerations or bleeding points. The mother, on questioning, did say the child gagged when the thermometer broke in the mouth.

"A flat plate of the abdomen and x-ray of the chest were taken and the radiologist reported small punctate radio-opaque metallic-like substances in the region of the stomach and a few minute-like densities seen in the lung field."

The November issue of the Journal of Pediatrics (Vol. 27, No. 5 pp. 733-737) contains a report by Drs. Schulz and Beskind on "Systemic Deposition of Metallic Mercury", including two case reports, one in a 4-year-old negro boy and one in an 11-year-old white girl.

In the first case the history did not elicit any information which could have suggested the entrance of metallic mercury into the body. The chief complaint on admission, the authors relate, was "falling, unconsciousness and jerking of the extremities" of one day's duration. X-ray examination of the skull, neck and trunk disclosed the presence of many small shadows of metallic density. Deposits were also noted in the heart, lungs, liver and soft tissue. A foreign body reaction surrounded the deposits. The portal of entry in this case is unknown.

A history of mercury ingestion was also not elicited in the second case reported by the author but the chest x-ray showed small round metallic densities in both lungs. A review of the patient's referral record revealed "peculiar shadows in the lungs" following a right cardiac catheterization and that no such shadows were present prior to the catheterization.

The authors conclude that negative physical examination and a negative history do not necessarily exclude metallic mercury deposition from consideration in a differential diagnosis of positive x-rays, that chronic systemic toxicity is not usually reported in cases of metallic mercury deposits and, that in anaerobic blood sampling, mercury may accidentally be introduced into the punc-

tured vessel. We have had reports of accidental introduction of mercury through the breaking of diagnostic apparatus used for tracheal/esophageal examinations without any untoward symptoms of mercury poisoning.

The knowledge that no injury will occur in such cases should result in a desirable decrease in x-ray examinations. However, the physician must bear in mind that mercury as vapor is highly toxic.

Substance Ingested: "Ant Button" *Age*: 15 months

This 15-month-old child, while playing on the floor in the kitchen, obtained an "Ant Button" containing sodium arsenate. The mother observed the "Ant Button" in her mouth, took it from her and gave her some milk. The child soon began to vomit, and was taken to a hospital emergency room where gastric lavage was done.

The hospital, located in New Jersey, called the New York City Poison Control Center for aid in identifying the ingredients of the product. The information was provided promptly and the patient was treated with BAL and intravenous therapy. Since the patient had repeated episodes of convulsions, she was placed on the critical list. She soon responded well to therapy and after one week in the hospital was discharged as cured.

"Ant Button" is a trade-name for an insecticide which uses crown bottle caps as containers. It is regrettable that the regulatory authorities have seen fit to permit this type of container to be used for a household insecticide.

Substance Ingested: "Ant Button" *Age*: 14 months

The nurse who interviewed the patient's family relates that they live in a basement apartment and that the furnace exploded and water leaked all over the apartment. The "Ant Button" which had been placed beside the water tank near the furnace must have floated from the furnace room past the baby who grabbed it and ingested the contents, while the mother was busily engaged elsewhere about the house. The mother immediately rushed the child to the hospital, about 15 minutes following ingestion. Although there were no apparent symptoms, besides constant crying, the patient was observed in the hospital three days prior to discharge.

Substance Ingested: Tincture of Arnica *Age*: 14 years

The patient, a 14-year-old female, stated she fell from a window while hanging curtains and bruised her body. She purchased the medication—arnica—from a drug store in order to treat the injury.

Thinking that the medication was to be taken orally, she ingested one tablespoon of the tincture on Monday; the second one two days later, on Wednesday; and began to feel ill a day following the second ingestion, on Thursday. When seen at the hospital, the patient complained of severe dizziness. After 2 hours of observation in the emergency room, she was sent home with instructions to report the following day but she never returned.

Tincture of arnica is probably unfamiliar to recent medical graduates. It is a tincture of the flower, Arnica montana, with a reputed therapeutic effect for sprains and muscular pains. The chemistry of the active constituents is still somewhat vague. The ingestion of this product can result in collapse and even death. When an overdose is taken, violent gastroenteritis may occur. The most common symptoms encountered in severe cases are pains in the stomach, vomiting, diarrhea, giddiness, intense muscular weakness and, finally, collapse. In some cases, the symptoms are chiefly of cerebral origin without any gastro-intestinal manifestations as was observed in this case. When used locally, severe dermatitis may result.

Symptomatic and supportive therapy are indicated. However, some authors have recommended the use of intravenous fluids to combat the dehydration and for the dilution of the toxin excreted by the kidneys. Attention must be paid to the maintenance of an electrolyte balance.

Although physicians rarely prescribe this product, pharmacists stock it and recommend it as an over-the-counter item. The continued use of archaic medications is still an annoying problem to the modern physician.

125 *Worth St., New York* 13

(This is the third of a series of papers by Dr. Jacobziner).

Use of a New Intestinal Motility Inhibitor for Treatment of Diarrhea in Children

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Thihexinol methylbromide, a new parasympathetic blocking agent, has been reported to act with relative specificity on gastrointestinal motor function. Oral doses of the drug, producing no significant suppression of gastric secretion, cause marked prolongation of gastrointestinal transit time[1]. Demonstration of its dominant antimotility action led to trials of thihexinol for the nonspecific treatment of diarrheal states, and preliminary clinical evidence of the drug's antidiarrheal efficacy was noted by investigators[1,2] who originally studied the compound under its experimental designation, Sch 2868. The present study had to do with a further evaluation of thihexinol for symptomatic control of diarrhea.

Material and Method

Observations were carried out in 153 children mostly with acute types of diarrheal disorders. The age spread among these patients was from two weeks to 12 years, and the mean age, reflecting the preponderance of infants in the group, was approximately 18 months. Clinical diagnoses of nonspecific enteritis, primary or secondary to acute upper respiratory infections, were made in the large majority of cases. In the remainder, diarrhea was attributed to food allergy, the coeliac syndrome, or other undetermined causes. Most patients were seen shortly after the onset of their diarrheal symptoms but, in a minority of the group, diarrhea had been a more or less chronic complaint. The criterion of diarrhea in all cases was the occurrence of more than four watery stools a day.

On admission to study, all patients were treated on a random basis either with thihexinol methylbromide** or, for the purpose of control, with a kaolin-pectin suspension†. Thihexinol was administered in the form of a palatable solution usually four times a day

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**Supplied as Entoquel® by White Laboratories, Inc., Kenilworth, N. J.
†An aqueous suspension containing 5.8 Gm. kaolin and 0.13 Gm. pectin per 30 cc.

and, depending on the patient's age, in approximate doses of 2.5 to 7.5 mg. The kaolin-pectin suspension was given in multiple daily doses of 5 to 15 cc. It should be emphasized that in contrast to the dietary measures ordinarily employed in pediatric management of acute diarrheas, namely, the proscription of solid foods and the use of boiled skim milk, practically all patients were kept on the usual diets.

Effectiveness of treatment in each case was measured by the length of the interval between the start of therapy and the control of diarrhea. The criterion of symptomatic control was the evacuation of a well-formed stool and the subsequent continuance of normal bowel function. The response to treatment was considered *excellent* when diarrheal control, as defined above, occurred in the first 24 hours, *good* when control was accomplished within 24 to 48 hours, *fair* when 48 to 72 hours elapsed before symptomatic control was attained, and *poor* when diarrhea persisted longer than 72 hours.

RESULTS

After three-day to five-day courses of treatment with the kaolin-pectin suspension proved ineffectual in 41 patients, the further use of this preparation was abandoned. Trials of thihexinol were initiated in this series of cases following withdrawal of the kaolin-pectin mixture. The subsequent order of antidiarrheal response to thihexinol in these cases, expressed in terms of the previously described gradients, is summarized in Table 1.

TABLE 1

Response to Thihexinol in Cases of Diarrhea Uncontrolled by Kaolin-Pectin Therapy

Total Cases	Antidiarrheal Response Number (and Percent) of Cases			
	Excellent	Good	Fair	Poor
41	17 (41%)	14 (34%)	3 (7%)	7 (17%)

The remaining 112 patients were treated with thihexinol from the outset. The scored symptomatic response to the drug in these cases, set forth in Table 2, did not differ substantially from that observed in the smaller series of cases in which thihexinol had been

substituted for the ineffectual kaolin-pectin preparation. Of the entire group of 153 patients who were treated with thihexinol, the antidiarrheal response was good-to-excellent in approximately 80 per cent.

TABLE 2

Response to Thihexinol in Cases of Previously Untreated Diarrhea

Total Cases	Antidiarrheal Response Number (and Percent) of Cases			
	Excellent	Good	Fair	Poor
112	48 (43%)	44 (39%)	15 (13%)	5 (4%)

SIDE EFFECTS

The only side effect noted during treatment with thihexinol was an infrequent, mild flushing of the skin in younger infants. This more or less transient erythematous reaction occurred in 6 (4 per cent) of the total cases, was eliminated by decreasing the dosage, and did not necessitate discontinuance of the drug.

COMMENT

In several of the cases in which thihexinol failed to control the diarrhea within 72 hours, the initial dosage of the drug was then doubled. The increased dosage was well tolerated and there was marked symptomatic improvement in the following 24 hours. This suggests that, at least in some of the poorly responsive cases, a higher initial dosage of thihexinol might have effected an earlier control of the diarrhea.

Worthy of mention, too, is that stool frequency and consistency were decidedly improved in the majority of patients during the first 24 hours of thihexinol therapy. However, since anything short of complete symptomatic control in diarrheal states is difficult to quantitate, partial improvement was not considered in the scoring of the antidiarrheal responses tabulated above.

None of the 153 patients treated with thihexinol required hospitalization for parenteral management of dehydration. Moreover, maintenance of usual dietary intake in almost all of these cases did not appear to delay or decrease the antidiarrheal response to thihexinol.

SUMMARY AND CONCLUSION

(1) The use of thihexinol methylbromide (Entoquel®), a new intestinal motility inhibitor, was evaluated in the symptomatic treatment of mostly acute types of diarrheal disorders in 153 children. The mean age in this group of patients approximated 18 months.

(2) The criterion of antidiarrheal response was the evacuation of a well-formed stool with subsequent normal bowel function. The response was considered *excellent* when diarrhea was controlled in the first 24 hours of treatment, *good* when control was accomplished within 24 to 48 hours, *fair* when 48 to 72 hours elapsed before symptomatic control, and *poor* when diarrhea persisted longer than 72 hours.

(3) In 41 cases, treatment with thihexinol was initiated after prior use of a kaolin-pectin suspension had proved ineffectual. The antidiarrheal response to thihexinol was *excellent* or *good* in 31 of these cases.

(4) In the remaining 112 cases, treatment with thihexinol was employed from the outset. Symptomatic response was *excellent* or *good* in 92 of these.

(5) The only side effect noted during thihexinol therapy was a mild, more or less transient flushing of the skin in 6 (4 per cent) of the total cases.

(6) The reported observations indicate that thihexinol is an efficacious and well-tolerated drug for the nonspecific treatment of diarrhea in children.

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407 University Avenue, Syracuse, New York

Pediatric Conference . . .

ST. LUKE'S HOSPITAL, NEW YORK
OCTOBER 4, 1960

J. Frederick Eagle, Jr., M.D., *Director of Pediatrics, Presiding*
Michael R. Dubin, M.D., *Medical Intern*
Veronica Petersen, M.D., *Pediatric Resident*
Edward H. Reisner, Jr., M.D., *Assistant Attending Physician*
Adoree Quero, M.D., *Pediatric Intern*

Dr. Dubin: J. R., SLH #42-62-51, is a ten year old, white male who was in excellent health until 1½ years prior to this admission at which time his Mantoux test became positive. He was placed on isoniazid (INH) and para-amino-salicylic acid (PAS) and did well until his present illness. About twenty-four hours prior to admission he noted a rash in his right antecubital fossa which, he was told by a pharmacist was due to bleeding into the skin. This didn't faze the boy, he managed to get into a fight that day and subsequently was covered with petechial and ecchymotic rashes. The physical examination was otherwise unremarkable.

The platelet count at the time of admission was approximately 50,000. Hemoglobin was 12.3. White Blood Count was 8,150 with 58 polys, 32 lymphs, 8 monos, and 2 eos. The tourniquet test was positive, and the Bleeding time was 1 minute 5 seconds. Clotting Time: 5 minutes 55 seconds. Prothrombin Time: 15.8 seconds, and 38.3 seconds when diluted, giving 64% activity. The clot did not retract. The LE prep was negative three times. A bone marrow done on the day after admission revealed the megakaryocytes to be normal but the platelets being formed were decreased.

Since it was impossible to decide whether this child had idiopathic thrombocytopenic purpura (ITP) or a para-amino-salicylic acid (PAS) or isoniazid (INH) sensitivity it was decided to withhold the PAS and see how the child reacted. After three weeks there was no significant change in his platelet count, which varied between 16,000 and 100,000. During this time his petechiae and ecchymoses disappeared. Three weeks after admission we

started 32 mg. of Meticorten and when this did not produce a significant platelet elevation we increased the Meticorten to 60 mg. a day. The platelet count rose to 240,000 in one week, after which the Meticorten dosage was decreased gradually and discontinued after two weeks, with no subsequent fall in the platelet count.

DR. EAGLE: Dr. Petersen, would you discuss our experience with idiopathic thrombocytopenic purpura?

DR. PETERSEN: In the past ten years we have seen fifteen patients on the Pediatric Service with idiopathic thrombocytopenic purpura. The patients ranged in age from nine months to eleven years. Hemolytic streptococcus was isolated from the nose and throat of one patient, and one child had German measles one week prior to admission. There were no other potential predisposing factors. In no instance was there any family history of bleeding. The duration of illness prior to admission in eleven of them was between one and four days. Five of the fifteen children were significantly anemic, however, at least one child probably had an iron deficiency anemia. The lowest hemoglobin on admission was 4.2 grams and this child died on the tenth day, the only death in our series. Platelet counts ranged from 5,000 to 70,000 with an average of about 20,000 to 30,000. The Rumpel-Leede Test was positive in all instances where it was performed. Clotting time was usually normal. Bleeding time was normal in over half and elevated in the rest, the highest value being 15 minutes. Clot retraction was usually abnormal. It was performed in nine patients, was normal twice, and there was no retraction in 24 hours in seven cases. All fifteen patients had epistaxis. In addition, five bled into the skin, three had hematuria, and one had vaginal bleeding. Bone marrows were done in 14 of the 15 children; four were normal, six had increased megakaryocytes, two had decreased megakaryocytes, and in four the megakaryocytes were believed to be immature. It took from two days to 12 weeks for the platelets to return to normal values. Twelve of the 15 patients received steroids or ACTH and of these twelve, seven showed an increased platelet count shortly after steroids were started. Three showed no response to steroids and two had a questionable response. Five of the 15 required a transfusion, one had a splenectomy. The child who received the splenectomy had had many previous admissions for ITP. Currently, post-splenectomy the platelets are still low, running between 60,000 and 80,000.

There was one death in this series. This child was nine months old and died on the tenth day of illness. Autopsy revealed hemorrhages throughout the body, mainly the viscera and the brain. This child had been given seven transfusions and had received ACTH during the last three days of his life.

DR. EAGLE: In any of the patients was there a good history of either drug ingestion or ingestion of other potential toxins?

DR. PETERSEN: I looked for this. Many of them had an aspirin or two in the week preceding hospitalization but this was not considered significant. None of our patients were known to have received any known bone marrow depressant.

DR. EAGLE: In my experience, in spite of what the textbooks say, drugs and chemicals have rarely been incriminated. Would you like to comment, Dr. Reisner?

DR. REISNER: Our experience with adults has been similar to that of Dr. Eagle's. More patients seem to have idiopathic disease than have thrombocytopenia which is frankly traceable to a toxin. On the other hand, one has to be quite alert to be able to pick up a toxin. I remember one case that we saw at Bellevue where a mother had sprayed the children with DDT in order to keep off the mosquitos. It was not until this mother brought in a second child with thrombocytopenia that we elicited this history.

A great many of the so-called idiopathics actually turn out later on in life to have lupus. This is particularly true of girls and it is always worthwhile to do L.E. tests on these patients. If the L.E. tests are negative they should be repeated after the patient has been on steroids two or three days. We have had the experience in the Department of Medicine of having obtained positive L.E. tests after several negatives, after steroids were begun. I think there is a rational explanation for this: that the steroid probably inhibits the action between antigen and antibody with the result that antigen accumulates in the patient's circulation and is available to produce a positive L.E. test.

As far as the treatment of ITP is concerned, in children it is a great deal more expectant than it is in adults. It is interesting that only one of your children came to splenectomy. In an adult group there is a much higher incidence of splenectomy. With adults, my rule of thumb is to start steroids and if the patient does not respond after having been given adequate dosage for a period

of three or four weeks to do a splenectomy. After splenectomy we can usually control the situation either without steroids or with a small dose.

In children, I feel that spontaneous recovery is the rule and I like to treat them expectantly for a while unless they are having hemorrhagic manifestations. If they are bleeding they should be given steroids for safety's sake in the hope of preventing hemorrhage in the central nervous system. It is certainly true that if they respond quickly to steroids one does not know whether the response is spontaneous or due to the steroid, but I do not think we have any right to take the chance if the patient is having symptoms.

This young fellow who was presented today was doing quite well and I felt that it was worthwhile waiting to see if he would respond to the withdrawal of isoniazid and PAS. At first it looked as though he was getting better, but later he relapsed and it became apparent that he probably had ITP.

What are the pros and cons of steroid therapy? There are two schools of thought. Some people have the feeling that there is more hazard in continued use of steroid therapy than there is in just letting a child with 75,000 to 80,000 platelets go without any therapy at all. If I had any guarantee that a patient's platelet count was going to stay at 75,000 to 80,000 I might be content to let him go untreated, but if, by giving him a small dose of steroids we can bring his platelet count to normal, I think we have a greater margin of safety. Moreover I feel that many of these patients' illnesses are due to hypersensitivity states, of which lupus is a classic example. If one has a chronic hypersensitivity state we must keep it under control until it runs down, and this running down may take as long as a year or two. I am quite prepared to use a small maintenance dose—not enough to cause side effects—over a period of two or three years.

In a child, how long should one wait before doing a splenectomy? Again, there is no hard and fast rule and much depends on the symptoms and whether the platelet count is running consistently below 50,000 or whether it is hovering around 70,000 or 80,000, allowing some margin of safety. Remember that we cannot keep children wrapped in cellophane all the time. They are going to have falls; they are going to get hit over the head with various things; and if they have idiopathic thrombocytopenia and are

exposed to trauma of that sort they may have serious internal hemorrhage. If good results are not attained with steroids within a matter of two or three months then a splenectomy should be done. After the spleen is removed it may take a year or more before the patient regains a normal platelet count.

We have seen cases in our Hematology Clinic, two adults and one child within the last year, who have shown a delayed return of the platelet count to normal following splenectomy. In one man it was only after a year that the count returned to normal. There was another adult a few years ago who went about six or eight months before her platelet count finally came back to normal.

DR. PETERSEN: Do you recommend platelet concentrate transfusions?

DR. REISNER: No. I think that fresh whole blood is a great deal simpler to administer. In the process of separating platelets from whole blood the platelets are traumatized and much time consumed so that probably only half of the platelets, or even less, will actually survive reinjection. It is much simpler to draw fresh blood in plastic containers and transfuse as quickly as possible. Under such circumstances there will be almost 100% survival of the platelets in whole blood.

DR. EAGLE: I would like to add just one thing. I am delighted to hear that out of fifteen cases only one splenectomy was done. I would disagree somewhat with Dr. Reisner on the indications for splenectomy in children but perhaps it is because I am prejudiced by an experience with an adolescent girl who had had her spleen removed electively some time earlier. This had been followed by a rise in the platelet count which only lasted for a few months. During her first menstrual period, which lasted for several weeks, she practically bled to death on numerous occasions and finally required a hysterectomy. Until the menstrual cycle has been fairly well established, girls with ITP frequently have major hemorrhages. In this case had a splenectomy not been done earlier, and reserved for such a crisis, I believe that the hysterectomy might have been avoided. I feel that a splenectomy should be reserved for major hemorrhagic manifestations that cannot be controlled in any other way. Dr. Quero is going to discuss the general diagnosis of bleeding disorders.

DR. QUERO: Table I gives a very simplified outline of what occurs after a traumatic injury which causes bleeding.

TABLE I

A. Vasoconstriction

Platelets release serotonin causing capillary constriction.

B. Fibrin clot formation

1. Platelet thromboplastic factor.
   Antihemophilic Globulin (AHG).
   Plasma thromboplastin component (PTC).
   Plasma thromboplastin antecedent (PTA).
   $\xrightarrow{Ca^{++}}$ Thromboplastin

2. Prothrombin
   Factor V
   Factor VII
   $+$Thromboplastin $\xrightarrow{Ca^{++}}$ Thrombin

3. Fibrinogen $+$ thrombin $\longrightarrow$ fibrin

Serotonin, a chemical vasoconstrictor is released from the platelets into the surrounding area, effectively slowing blood flow and thereby permitting the formation of a clot.

Fibrin clot formation proceeds in three stages. Stage I is the formation of thromboplastin. This requires a platelet thromboplastic factor, antihemophilic globulin (AHG), plasma thromboplastin component (PTC), and plasma thromboplastin antecedent (PTA). These four factors in the presence of ionized calcium react to form thromboplastin.

Stage II is the conversion of prothrombin into thrombin. Again ionized calcium is needed and the thromboplastin that was formed in Stage I is used. Two other plasma constituents are thought to play a role in the production of thrombin. One is Factor V and the other is Factor VII. Factor V is also known as proaccelerin, accelerin, or labile factor; and Factor VII as proconvertin, convertin, or stable factor.

In Stage III fibrin is formed from fibrinogen using the thrombin which was formed in Stage II. This scheme is a greatly oversimplified account of the mechanisms of coagulation but considerably aids the understanding of the laboratory tests to be discussed.

Laboratory examinations may be divided into three groups, listed in Table II, which will determine the general area of dysfunction. The first group of tests determines the effectiveness of capillary function, the second the presence and normal function of platelets, and the third the effectiveness of clot formation.

The bleeding time is primarily a measure of the capillary response to injury. Since this capillary response is elicited through serotonin any thrombocytopenia where there is not enough serotonin being given off by platelets yields a prolonged bleeding time. Any primary disease of capillaries, as Von Willebrand's Disease, will yield a prolonged bleeding time. Scurvy, which is basically an absence of intracellular cement, will also have a prolonged bleeding time. Any very severe deficiency of one of the blood factors as opposed to the capillary factor will also yield a bleeding time which is prolonged, but the deficiency must be severe. Mainly, the bleeding time measures the capillary response and since this is due to serotonin it will be abnormal with thrombocytopenia.

TABLE II

Capillary Function

Bleeding time
Tourniquet Test

Platelet Function

Platelet Count
Clot Retraction

Clot Formation

Clotting Time
Screening Test
Fibrinogen Level
Prothrombin Time
Prothrombin Consumption Test

Another measure of the capillary factor in hemorrhage is the tourniquet test, also known as the Rumpel-Leede Phenomenon or capillary fragility test. A blood pressure cuff is placed around the arm and inflated to a pressure half-way between the systolic and diastolic blood pressures. Four centimeters from the antecubital fossa a circle 5 cm. in diameter is drawn on the arm. The blood pressure cuff is left in place for eight minutes, and five minutes after it is removed the petechiae are counted. Normally there should be less than ten petechiae in the circle. Scurvy will yield a positive tourniquet test. Since the platelets somehow function to maintain support of the capillaries, this test will be positive whenever there is a platelet deficiency.

Platelet count measures platelets directly. Normal values in an adult are 140,000 to 340,000 per cubic mm. In the newborn values

are lower—100,000 to 250,000 per cubic mm.—and normal adult levels are not attained until three months of age.

Clot retraction is also a measure of platelet function and should be performed as well as a platelet count since failure of clot retraction when the platelets are present in normal amounts is indicative of platelet dysfunction and diagnostic for thrombasthenia. It is very simple to determine clot retraction. The clot of venous blood will normally retract in 30 to 60 minutes. (In the patient just presented it never retracted.) When the platelet count is under 70,000 it will not retract.

A prolonged clotting time, or a failure of blood to clot, indicates a deficiency of one of the four factors necessary for thromboplastin formation, or a deficiency of prothrombin, Factor V, Factor VII, or fibrinogen. Venous blood and not capillary blood must be used in order to avoid tissue thromboplastin contamination during finger-pricking which would obscure any abnormality in Stage I. 1 cc. of venous blood is placed in each of three 10 x 75 mm. tubes. After three minutes the first tube is tilted every half minute until it can be inverted without spilling, in other words, until it has clotted. Since agitation of blood promotes clotting, the other two tubes usually will not have clotted by this time, and the tilting is then continued with the second tube, and after it clots, with the third tube. The clotting time is the length of time it takes for the third tube to clot—normally about five to ten minutes. This is a very crude test for all the factors of coagulation. However, since most of the blood factors are present in excess amounts, a partial deficiency may not be detected by the clotting time determination. For example, the classical paradox of thrombocytopenic purpura is a prolonged bleeding time and a normal clotting time or coagulation time. Evidently there are not enough platelets to supply the serotonin for vasoconstriction but there are enough platelets to supply the platelet factor to trigger off the mechanism of blood clotting itself. However, in hemophilia, or AHG deficiency the clotting time is prolonged. Likewise, there will be a prolonged clotting time in PTC deficiency, PTA deficiency, hypofibrogenemia, and hypoprothrombinemia. Another cause of prolonged clotting is the presence of an anticoagulant such as heparin or dicumarol.

The screening test will distinguish between the presence of an anticoagulant and the absence of a coagulation factor. The test is performed with oxalated plasma. Oxalate and citrate both operate

to prevent coagulation of the blood by eliminating the calcium factor which is necessary in practically all of these stages. Oxalate precipitates the calcium, citrate prevents its ionization. The patient's plasma is serially diluted with normal plasma. Finally calcium chloride is added, which was the only factor removed with oxalate. If the patient's plasma is normal, all tubes will clot. However, if the basic defect is a deficiency in any plasma factor the clotting time in the undiluted patient's plasma will be abnormal, and the clotting time in the tubes diluted with normal plasma will be normal because of the fact that only minute quantities of normal plasma are necessary to make up the plasma deficiency of the patient. In other words, if AHG is deficient just 2/10 of a cc. of normal plasma will supply enough AHG so that all of these clotting times will be normal.

On the other hand if the defect is due to hyperheparinemia or to excess dicumarol therapy or to any anticoagulant the pattern will be different. The patient's undiluted plasma will still be abnormal but the rest will all become progressively shorter as the anticoagulant is more and more diluted by the normal serum.

Finally, we must distinguish between a deficiency of prothrombin, Factor V, Factor VII, AHG, PTC, and PTA. Fibrinogen can be measured directly. The prothrombin time detects the presence or absence of prothrombin, Factor V, and Factor VII. In other words, calcium and thromboplastin are both supplied and the clotting time is measured. Although called the prothrombin time, it is as much a Factor V time and a Factor VII time as a prothrombin time since any of these deficiencies will be manifested by poor clotting.

In order to differentiate between these deficiencies an attempt is made to correct the abnormal prothrombin time by the addition of one of these factors.

Normal serum contains Factor VII but prothrombin and Factor V are missing because they were used up in the clotting process. Thus if the addition of normal serum to the patient's plasma corrects the abnormal prothrombin time, the plasma was deficient in Factor VII.

Aluminum hydroxide treated plasma absorbs both prothrombin and Factor VII leaving Factor V. Therefore if aluminum hydroxide treated plasma corrects the abnormal prothrombin time, the patient's plasma was deficient in Factor V.

If neither normal serum or aluminum hydroxide treated plasma corrects the abnormal prothrombin time, the defect must be due to prothrombin deficiency.

Finally, having determined that there is no deficiency of fibrinogen, prothrombin, Factor V, or Factor VII, we are left with a diagnosis of a specific deficiency in Stage I where thromboplastin is found. To distinguish between AHG, PTC, and PTA deficiencies we utilize the prothrombin consumption test, which is sometimes called the serum prothrombin time.

In the prothrombin consumption test, blood is drawn, allowed to clot, and incubated for two hours at 37° C. If there is a deficiency of thromboplastin secondary to AHG, PTC, or PTA deficiency, the prothrombin will not be completely utilized, and a prothrombin time done on this serum will be short, indicating decreased prothrombin consumption, which is another way of saying that there was insufficient thromboplastin generated. It should be emphasized that in the prothrombin consumption test, or serum prothrombin time, a normal time is greater than 25 seconds and an abnormal serum prothrombin time is short, less than 25 seconds.

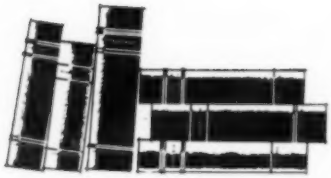
Again, as in the plasma prothrombin time, we attempt to correct an abnormal serum prothrombin time by the addition of the missing factors.

If normal fresh plasma is treated with barium sulfate, prothrombin and PTC will be removed. Forty-eight hour old normal serum will not contain AHG since it will have been completely utilized by clot formation and because it is a labile factor.

Therefore if the addition of barium treated fresh normal plasma to the serum being tested results in a prolonged serum prothrombin time, and the addition of forty-eight hour normal serum results in a short serum prothrombin time AHG must be deficient.

If the addition of barium sulfate treated plasma does not prolong the serum prothrombin time, but forty-eight hour old serum does, PTC must be deficient. If both barium sulfate treated plasma and forty-eight hour old serum result in a prolonged serum prothrombin time, PTA is presumably deficient.

With these nine relatively simple tests, 95% of all bleeding disorders may be diagnosed.



. . . Books

Edited by

MICHAEL A. BRESCIA, M.D.

EARLY IDENTIFICATION OF EMOTIONALLY HANDICAPPED CHILDREN IN SCHOOL. By ELI M. BOWER. Cloth. Pp. 120. Charles C. Thomas, Springfield, Ill. 1960. $5.50.

The author has demonstrated in this small but valuable volume the need and possibility of detecting emotional problems early during the school career. The teacher who sees the child for a longer time than even the parents under varying conditions is in a strategic position to detect the child with an emotional handicap, as the author prefers to call emotional problems. The book then is primarily addressed to the teachers to help them detect emotionally handicapped children early in school life. This is done by direct screening devices and various other methods as the author indicates in the Appendix to his book, such as "A Class Play" in which the pupils choose their roles and the roles of their classmates in a fictitious play and "Thinking About Yourself".

"The significant characteristics of children indicating a need for closer scrutiny by a teacher are: inability to learn, unsatisfactory interpersonal relationships, inappropriate behavior, unhappiness and repetitive illness". This succinctly guides the teacher as to which child needs further evaluation.

This book is highly recommended not only to teachers but to School Health personnel both nurses and physicians. They will find this easily read volume of interest and value. The author writes with understanding and keen sense of humor as illustrated by dedicating the book to "Barbara who sharpened the pencils, Kenneth who ate the erasers, and Phyllis who did the work".

M. A. B.

HEGGLIN, R.: Differentialdiagnose innerer Krankheiten. (Differential diagnosis in internal medicine). G. THIEME. Stuttgart. 7th ed. (1960). $18.75.

This is the 7th (German) edition of a book which was also published in Italian (three editions), Spanish, Polish and Greek. Among its most important features are illustrations, a great many

of them multicolored, which makes it a pleasure and a stimulating experience even to leaf through the pages. However, this volume is not only an excellent atlas of internal medicine, but also something like a medical encyclopedia and a medical dictionary, providing a vast panorama of facts and problems. The brief historical data is included. The immense material surveyed is arranged from a clinical point of view, considering complaints of the patient, like "fever," "headache," "dyspnea," "pain in the thorax," "abdominal pain," "pain in extremities," etc., or from a point of view suggested by results of the first medical examination, such as "disturbances of cardiac rhythm," "cyanosis," "anemia," "arterial hypertension," "arterial hypotension," "pulmonary condensation," "enlargement of the hilus," "enlargement of lymph nodes," "splenomegaly," etc. Indeed, this dichotomy causes quite a few repetitions, which, however, may prove useful for the student. The book contains also a few chapters in which classic problems of internal medicine, like "hemorrhagic diathesis," "icterus," or "edema" and "disturbances of the water and electrolyte metabolism," etc. are comprehensively reviewed. This volume will be of excellent service to medical students who like to see the questions of their examiners and the correct answers systematized, and also to practitioners who need immediate information. For thoughtful readers, it is a significant record reflecting contemporary German medicine and teaching methods.

PHILIP SCHWARTZ, M.D.

MENTAL RETARDATION IN INFANTS AND CHILDREN. By ABRAHAM LEVINSON, M.D. (Deceased) and JOHN A. BIGLER, M.D. Cloth. Pp. 308. The Yearbook Publishers, Inc., Chicago, Ill. 1960. $8.00.

This compact book is addressed to all practicing physicians. It concerns the problems presented by the non-institutionalized retardate as seen by the two author-pediatricians in their private practices and as studied at the Dr. Julian D. Levinson Research Foundation at the Cook County Hospital of Chicago.

Emphasis is placed on the brain, its anatomy, growth and chemistry as they are determined by heredity, environment, nutrition, and biochemical factors. The preface states, "Physicians for centuries have concentrated their attention on bone, muscle, and the contents of the thoracic and abdominal cavities". It asks, "Why did men consider the mind so unrelated to the brain and why were mental processes thought to be outside the realm of medicine?" And it

adds, "Whatever the explanation we have at last entered a new era". Indeed, this book focuses on the brain as a physical organ of the body with detail and comprehensiveness. It discusses fully medical prognosis and therapy.

While speech and hearing receive recognition in a separate chapter, vision is very briefly treated. This is surprising since its importance in mental retardation is considerable. A special chapter is devoted to psychological testing but the discussion is limited to children whose behavior has reached the level of at least two years. Evaluation techniques such as the Vineland Social Maturity Scale and the Merrill-Palmer Scale are not even mentioned. Psychological or developmental examination of the infant and young retardate is sketchily discussed in the 8 page chapter on diagnosis. Thus the book would need to be supplemented with other references. It might be said that these topics need not concern the pediatrician but surely vision is in his realm. Furthermore, since mental retardation is frequently manifest primarily in behavior development the physician who is responsible for diagnosing the retardation should be familiar with the means of diagnosis, their values and limitations.

Thus, while there are some omissions which this reviewer deplores, the main purpose of the authors has been accomplished. The book is unique in its full concise enlightenment of a subject which physicians have not encompassed in their practice. They will welcome the book as part of their armamentarium.

HELEN THOMPSON, Ph. D.

THE DEVELOPMENT OF THE INFANT AND YOUNG CHILD, Normal and Abnormal. By R. S. Illingworth, M.D., Cloth. Pp. 318. Price $6.50. Baltimore: William & Wilkins Co. exclusive U. S. agents. 1960.

Dr. Illingworth, a pediatrician who is Professor of Child Health at the University of Sheffield, England, states he has written this book on child development because, "There are several excellent books on child development. . . . Most of them were written, however, by psychologists, and I feel that a book on child development should be written by a pediatrician".

As a psychologist whose work for many years has brought me into close contact with pediatricians both in private practice and in the lecture room, I applaud Dr. Illingworth's book. He gives a critical evaluation of current methods of assessing and predicting the development of young children, answering par-

ticularly the critics of the Gesell method. He concludes, "Developmental tests in infancy are of great value in that they can detect mental retardation and neurological conditions with a considerable degree of certainty".

Subsequent discussions cover those factors which affect mental development, the physical defects and diseases associated with mental development, the normal development of the young child with variations normal and abnormal, and how the pediatrician may himself evaluate this development with reference to the child's physical condition, history, and environment, stressing the importance of considering the child as a whole. Dr. Illingworth states: "I am convinced that the work of Arnold Gesell and others who have contributed so much to our knowledge of child development, is just as fundamental to anyone concerned with the care of children, and particularly to the pediatrician, as is anatomy to the surgeon".

The book is easy to read due to its clear type and format, its excellent organization, and its simple effective style. The photographic illustrations are of fine quality and well-chosen. Case material is presented from Dr. Illingworth's own experience. This book can be recommended most highly. It is scientifically sound and is valuable both as a readable text and a convenient reference.

HELEN THOMPSON, PH.D.

AUTHOR'S SUMMARIES

Feinstein, A. R., Taranta, A. and Di Massa, R.: ERRORS IN THE DIAGNOSIS OF ACUTE RHEUMATIC FEVER. (New York State Journal of Medicine 60:2835 Sept. 15, 1960).

In 12 per cent of 163 consecutive patients referred to Irvington House with a diagnosis of recent acute rheumatic fever, the modified Jones diagnostic criteria were not fulfilled. Seven per cent of the patients had had a self-limited, probably nonrecurrent, minor febrile illness. In the remaining 5 per cent, some other major organic disease was present.

Most of the diagnostic difficulties were caused either by failure to use the Jones criteria or by incorrect application of them. In the patients with minor illness the most frequent errors involved:

(1) the assumption that loud physiologic systolic murmurs were pathologic or that changes in the intensity of systolic murmurs represented carditis, (2) the assumption that premature cardiac contractions per se were due to carditis, (3) a too-narrow range permitted for normal temperature and sedimentation rate variations, and (4) too great significance given to rapid pulse rates measured while the patient was awake. In the patients with other major organic disease, the diagnostic errors usually arose because of failure to rule out alternative causes of fever or positive laboratory test results for inflammation, arthritis, and/or heart failure.

Errors in the diagnosis of rheumatic fever are now particularly important because of the widespread use of antistreptococcal agents to prevent recurrent attacks after the initial episode. If the original diagnosis was incorrect, the effect of the error is compounded by the subsequent administration of a long-term prophylaxis regimen which is unnecessary and which can have serious physiologic and psychologic consequences.

These errors can generally be avoided by using better judgment when the modified Jones diagnostic criteria are applied. Since clinical judgment has so many subjective variations a more objective approach is desirable. This can be achieved by insisting that evidence of a preceding group A streptococcal infection be made a prerequisite to the diagnosis of rheumatic fever. The streptococcal evidence can frequently be obtained from an initial throat culture and an antistreptolysin O titer. When these results are negative, positive results can be sought by measuring additional streptococcal antibodies and by testing consecutively drawn serum specimens. In a properly performed serial run, a failure to demonstrate a significant change in the antibodies would be strong evidence against a preceding streptococcal infection and would make the rheumatic diagnosis unlikely.

The measurement of additional antibodies and the performance of sequential serologic tests is done currently only as a research procedure at a few isolated institutions. If public health authorities could provide facilities for these tests and arrange to disseminate the use of them among physicians, the effects would inevitably help reduce the incidence of errors in the diagnosis of rheumatic fever.

News and Notes . . .

On March 7, 1961

One day symposium on "Mechanisms of Gastro-intestinal Absorption" under joint sponsorship of Johns Hopkins, School of Hygiene and Public Health and the National Vitamin Foundation, will be held at Hotel Sheraton-East, New York at 9 AM. No registration fee.

Clinical Symposium on Viral Diseases

Physicians attending the Clinical Symposium on Viral Diseases held in Miami in September heard reports of over 600 cases of various viral diseases which were treated with Reticulose, a lipoprotein-nucleic acid complex. The drug, either by its ability to inhibit the action of virus or by alteration of the host cell response in preventing virus multiplication, and its capacity to increase antiviral, antibody response, exerts a positive therapeutic effect in both acute and chronic infection. Reticulose, when administered in the acute stage, is reported to rapidly inhibit the course of herpetic diseases, infectious hepatitis, encephalitis, generalized vaccinia, influenza, including Asian influenza, infectious mononucleosis, upper respiratory viral infections, mumps orchitis and measles. Clinical improvement objectively and subjectively may be anticipated within 24 to 36 hours. Over 500,000 injections have been given with no reported toxic manifestation. The only contraindications were hypersensitization and active tuberculosis.

Pediatric Course

A continuation course in Pediatrics for General Physicians and Specialists will be presented from February 27 to March 1, 1961, at the Center for Continuation Study on the University of Minnesota campus.

The visiting faculty will include Doctors Edward A. Mortimer, Jr., Assistant Professor Pediatrics, Western Reserve University School of Medicine, Cleveland, Ohio; Irving Schulman, Director of Hematology Children's Memorial Hospital, Chicago; Robert J. Slater, Associate in Pediatrics, University of Toronto Faculty of Medicine, Toronto, Canada; and Associate, Sloan Kettering Institute for Cancer Research. The remainder of the faculty will include members of the faculty of the University of Minnesota Medical School and the Mayo Foundation.

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*Klein, B.: Antibiotic Med. 5:462 (July) 1958.

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1. Macy, I. G.; Kelly, H. J., and Sloan, R. E.: with the Consultation of the Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council: The Composition of Milks, Publication 254, National Academy of Sciences and National Research Council, Revised 1953. 2. Brown, G. W.; Tuholski, J. M.; Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: Evaluation of Prepared Milks in Infant Nutrition; Use of the Latin Square Technique, J. Pediat. 56:391 (Mar.) 1960.

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